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PROMISING COMPOUNDS FOR TREATMENT OF COVID-19

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ABSTRACT. *The study spans over-identification of phytochemicals suited for treatment of COVID-19. The study focuses on the chemical that has a tendency to bind with Human ACE2 protein and two of the main Sars-Cov-2 proteins which are the Spike protein and the RNA-directed RNA polymerase (RdRp) protein. After screening a large list of phytochemicals two of the compound i.e. Kansuinine B and Digitoxin were found to have promising traits for the treatment of COVID-19. Both the compounds have been in use for centuries. Digitoxin was extracted from Foxglove seeds in 18th century for heart-related illnesses. Kansuinine B originates from a Chinese herb Euphorbia Kansui (E. Kansui) E. Kansui has been widely used in herbal medicine for a multitude of illnesses including lungs related diseases. Studies also show that it has the ability to suppress cytokine response through the expression of the SOCS3 gene. In-silico simulations show that both these compounds have a better affinity and binding properties with these three proteins as compared to many other drugs under trial for COVID-19 like Remdesivir, Ritonavir, Famotidine, Camostat Mesylate, and Hesperidin. A treatment based on the combination of both compounds can be very effective. Any self-medication of both the compounds is highly discouraged as misuse of both the compounds can be very harmful.*

Keywords: COVID-19,In-silico prediction, protein-ligand interaction..

1. **Introduction. COVID-19** is the pneumonia caused by the virus called Sars-Cov-2. This virus belongs to the corona virus family. Previously known viruses of this family cause diseases like SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). Out of all these diseases COVID-19 has proven to be most infectious and deadly. It has the potential to spread at an exponential rate. If uncontrolled almost 70% of the population can get infected. Furthermore, the novel corona virus is greater threat because the population at large has never been exposed to this virus and hence have no immunity against it. The Coronavirus pandemic has emerged as one of the greatest challenge of the century.

Virus is an organism that lies at the edge life. It can be transmitted through several ways. Generally, they spread through air, water and bodily fluids like blood. Sars-Cov-2 is spread through the aerosol of infected person. Furthermore, it can live on surfaces on which droplets from coughing or sneezing of an infected person fall. On such surfaces the viral structure can survive for prolonged periods of up to 72 hours. Anybody who touches such a surface can get himself infected. Simplest preventive measure is to wash hands frequently and not to touch surfaces in public use.

Antibiotics are used to counter pathogens like bacteria but bears no effect on viruses. No medicine has been found that can kill virus and hence clear it from the system. Vaccines are used as a preventive measure. Basically, vaccines are deactivated pathogens which train the immune system to generate a response against them. This leads to generation of antibobies against the pathogens. Moreover, the B- and T-cells get trained to generate a immune response against these pathogens. Some of the infections like HPV and HIV can evade the immune response which makes it impossible to find a vaccine against them. Anti-viral drugs are used to cope with such situations. Anti-viral drugs mechanism works by targeting specific proteins of the viral structure. These proteins may either be linked with reproduction of virus or its underlying mechanism for entry into human cell structure. Anti-viral drugs interacts with key structural and non-structural proteins of the virus to inhibit its function. This inhibition prevents the virus to either replicate or damage human cells.

Phyto-chemicals are well tolerated substances which have been in use since centuries. Most of them are well tolerated and their side effects if any are well known. Many phyto-chemicals are known to have anti-viral properties. A range of potent phytochemical such as flavonoids, organosulfur compounds, lignans, terpenoids, sulphides, limonoids, polyphenolics, chlorophyllins, coumarins, furyl compounds, saponins, alkaloids, thiophenes, polyines, proteins and peptides have been found to have therapeutic effects against a cohort of viruses. Many public chemical databases like PubChem lists a large number of phytochemicals. Analytical and Laboratory trials require a long time taking process for finding appropriate drug. This process can be immensely expedited. This study uses efficient and accurate modeling techniques of simulating the effects of compounds on proteins. This method provides a faster and robust answer regarding the appropriateness of a chemical.

2. Materials and Methods Fundamental work regarding the discovery of these phytochemicals was obtaining the genome of the Sars-Cov-2 virus. Subsequently, the genomic primary protein structure as well as 3D structure has also been formed [1]. Fig 1. shows the 3D structure of genomic protein of Sars-Cov-2 while Fig2 shows the Spike protein of Sars-Cov-2.

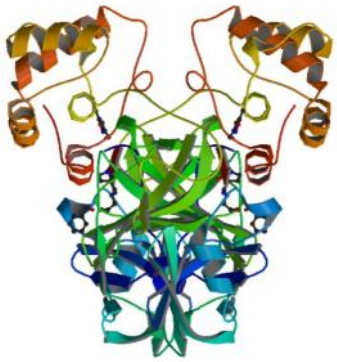


Figure 1 Genomic Protein of Sars-Cov-2

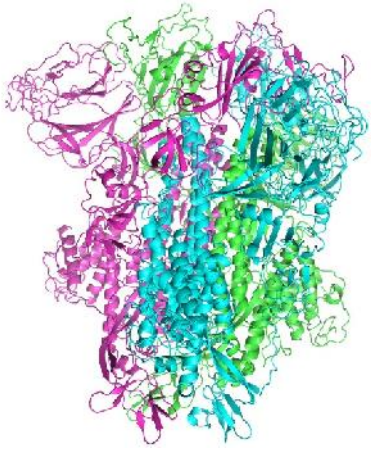


Figure 2 Spike protein of Sars-Cov-2

The spike protein of Sars-Cov-2 acts as a receptor for Human ACE2 protein given in Figure 3. The ACE2 proteins forms the outer membrane of the lungs. Fig 3 shows the 3D structure of ACE2 human protein.

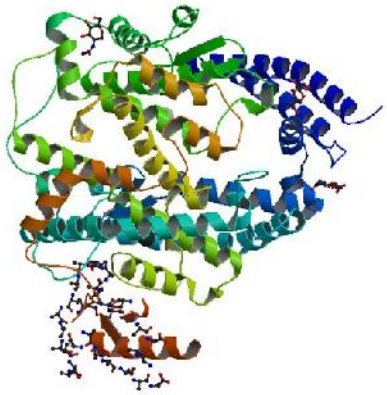


Figure 3 Shows the ACE2 Human protein

Once the virus gain entry into a cell it uses the cell resources to replicate itself making the cell sick and leading to its eventual death. The RNA structure of the virus is replicated by the RNA-directed RNA polymerase (RdRp) protein through its genome transcription. The tertiary structure of the RdRp protein is illustrated in figure 4.

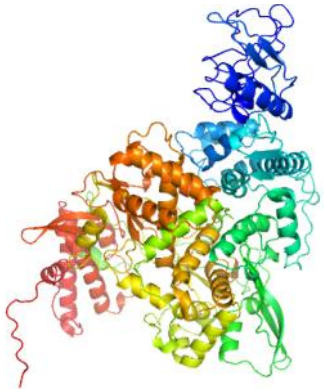


Figure 4 RdRp Protein of Sars-Cov-2

Numerous possibilities are explored to find a phytochemical that has antiviral effect against Sars-Cov-2. Phytochemicals that bind with the spike protein can prevent it from anchoring itself with the lungs, phytochemicals that binds with ACE2 protein also have same effect. The proteins that bind with RdRp protein can prevent replication of virus.

The structure of 2400 phytochemicals listed on PubChem [2] was used to compute their affinity with the three target proteins. To validate the work the affinity of currently under trail drugs for COVID-19 was also estimated. Many researchers have used mathematical and artificially intelligent models to study proteomic properties [3-28]. Based on virtual drug discovery models the listed phytochemicals were screened. Their affinity with the given three receptors was thoroughly probed. An affinity value of less than -7 is considered promising. Such promising compounds were further investigated for binding site attributes.

3. Results. The work focuses on discovering the most appropriate substance that could mimic an antiviral effect against COVID-19. It is about finding the right chemical or a combination of chemical which is like a brute force search. After thorough screening and detailed computational analysis two compounds were found to be promising with considerably better affinity. Furthermore, their interaction is compared with the interaction of other compounds being actively pursued in different trials like Hydroxychloroquine, Camostat Mesylate, Hesperidin, Ritonavir, Famotidine and Remdesivir. The two compounds identified are

1) Digitoxin (PubChem ID 441207)
2) Kansuinine B (PubChem ID 442050)

The affinity of compounds along with binding sites with RdRp, Human ACE2 and Spike proteins are listed in

Table1, 2 and 3 respectively.

Table 1 Binding of RdRp Protein with compounds

Ligand Name	Binding Residue 1	Distance Residue 1	Binding Residue 2	Distance Rsidue 2	Binding Afinity
Digitoxin	ARG-173	2.8	TYR-346	2.5	-10.3
Kansuinine B	TYR-69	2	ARG-118	1.4	-19.3
Camostat Mesylate	TYR 346	2	-	-	-6.8
Hesperidin	THR 394	2.5	PHE 396	2.7	-8.4
Ritonavir	ASP 208	2.5	SER 6	2.1	-8
Famotidine	ASP-760	2.5	TRP-800	2.2	-6
Remdesivir	ARG-249	2	ARG-349	2.2	-8.1
Hydroxychloroquine	GLY-327	2.7	HIS-347	2.3	-6.3

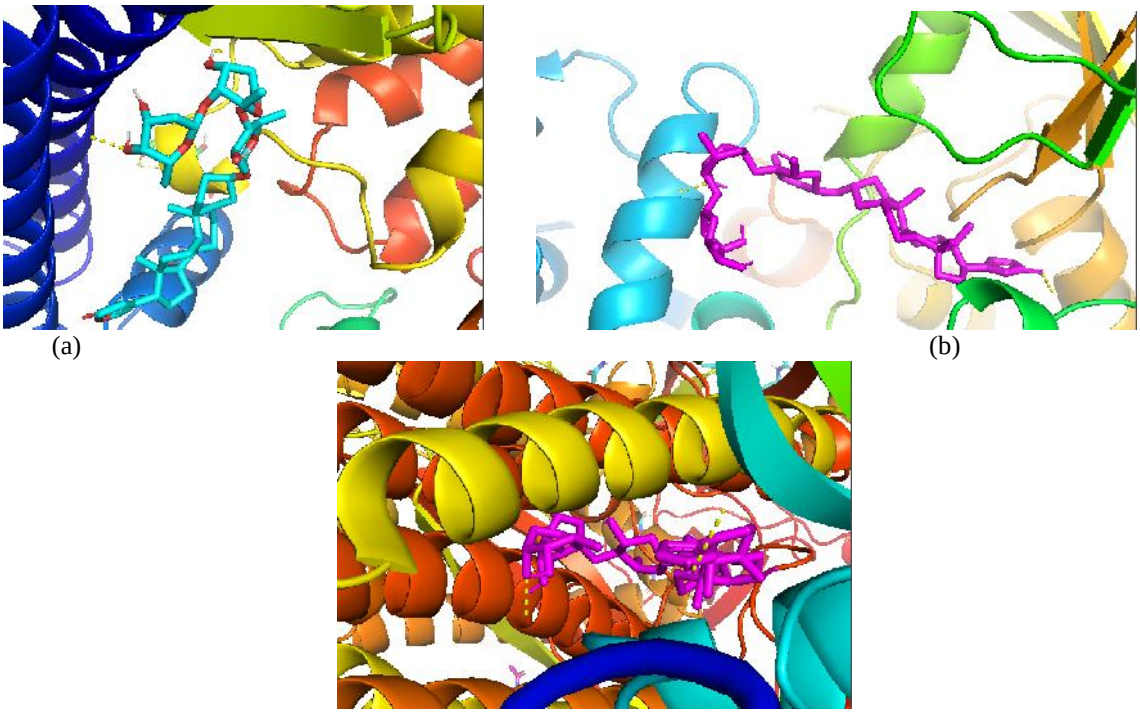
Table 2 Human ACE2 protein Bindings with compounds

Ligand Name	Binding Residue 1	Distance Residue 1	Binding Residue 2	Distance Rsidue 2	Binding Afinity
Digitoxin	ASP-349	2.2	SER-43	2.5	-10.7
Kansuinine B	ALA 348	2.8	SER 47	1.7	-17
Camostat Mesylate	TYR 385	2.1	LEU 73	2.9	-7.6
Hesperidin	ASP 382	2.6	LYS 562	2.1	-9.8
Ritonavir	ASP 350	2.4	SER 42	2.6	-8.8
Famotidine	ASP-543	2.8	SER-547	2.6	-6.2
Remdesivir	ARG-514	2.5	ASN-394	2.1	-7.7
Hydroxychloroquine	ARG-393	2.2	ASP-350	2	-6.4

Table 3 Interaction of Spike protein with compounds

Ligand Name	Binding Residue 1	Distance Residue 1	Binding Residue 2	Distance Residue 2	Binding Afinity
Digitoxin	ARG-1014	2.5	GLN-314	3.4	-10.2
Kansuinine B	THR 778	2.2	LYS 733	2.7	-18.9
Camostat Mesylate	ARG 1039	2.5	ASN 1023	2.1	-8.2
Hesperidin	GLN 1113	2.2	GLN 913	2.3	-9.7
Ritonavir	No Bonding		No Bonding		-8.3
Famotidine	ASP-745	2.7	CYS-743	2.5	-6.5
Remdesivir	TYR-756	2.9	ARG-995	2.5	-8
Hydroxychloroquine	ASP-350	3.5	PHE-970	2.5	-7

Above tables show that the affinity of Digitoxin and Kansuinine B are higher than other compounds being tested in various trials. Moreover, the effect of Digitoxin on Spike protein seems noteworthy as it binds to a huge span of the protein. This is a strong indication that Digitoxin can induce an active role in inhibiting the function of spike protein. Kansuinine B shows good ability to bind with HumanACE2 protein makes is suitable for prophylactic use. The binding of these compounds is illustrated in below diagrams.



(a) (b)

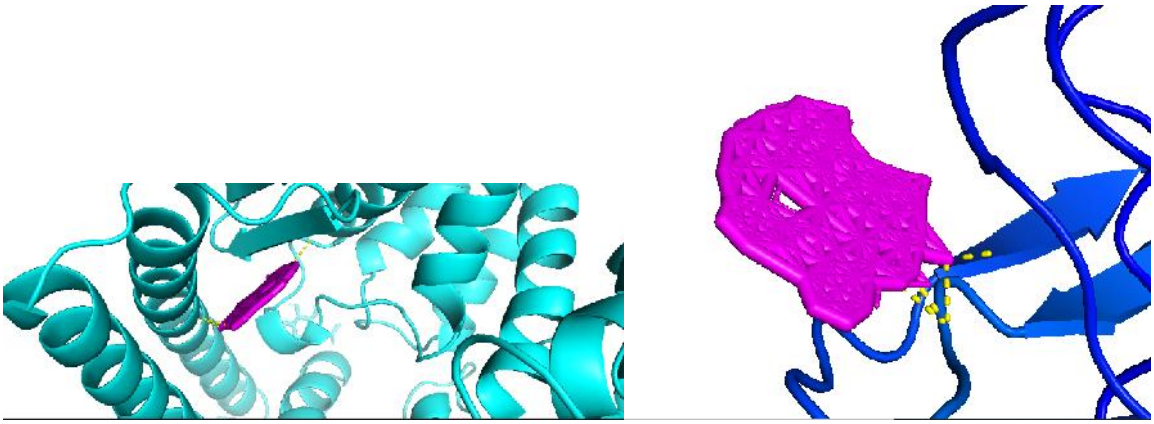
(c))

Figure 5 Interaction of Digitoxin with (a) RdRp, (b) Human ACE2 and (c) Spike proteins.

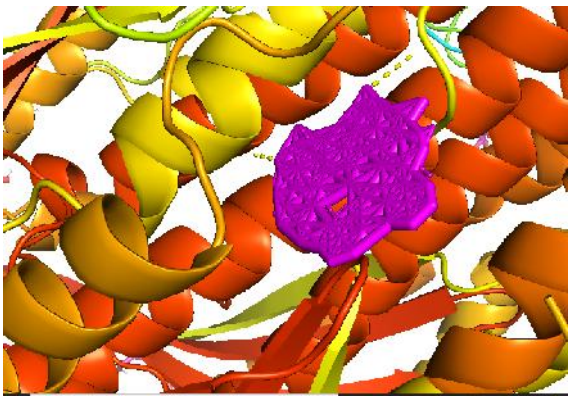
Conclusion. Simulations show that both the compounds have promising attributes which makes them a good candidate for the treatment of COVID-19. They have the highest affinity. Digitoxin and Kansuinine B binds to RdRp protein at different residue sites covering a significant part of protein. This suggests that their combined use can inhibit the operation of RdRp protein significantly. RdRp protein is responsible for replication of the virus once it gains entry into the cell. Inhibition of RdRp will impede this replication process. Moreover, Kansuinine B exhibits good binding with Human ACE2 protein. This indicates that that it also has prophylactic effect. A comparison of affinity and binding sites is shown for some other compounds currently subject of various trials. The overall comparison among these compounds indicates that both these compounds have highest affinity with key proteins and the combination is a potential drug for COVID-19.

Kansuinine B

Kansuinine B is diterpenoids found in the Chinese herb Euphorbia Kansui (E. Kansui), it is also locally called *Gan Sui*. In Chinese herbal medicine it has been used since ages for edema, cough, accumulation of pathogens in lungs, dysuria and constipation. One study shows that use of Euphorbia Kansui suppresses the Cytokine response through expression of SOCS3 gene. Immense cytokine response namely the *Cytokine storm* is considered as the main factor that causes death in old age COVID-19 patients [22]. Hence, this is another additional factor that supports the use of E. Kansui for COVID-19 treatment.



(a) ……..(b)



(c)

Figure 6 Interaction of Kansuinine B with (a) RdRp, (b) Human ACE2 and (c) Spike Proteins

Digitoxin

It is a compound found in an herb called Foxglove (*Digitalis Purpurea*). It was first extracted in 18th century to be used for heart condition. It was used for treatment of atrial fibrillation. Now its derivative Digioxin is used for the same purpose.

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